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HIV-associated Prospective Memory Impairment in the Laboratory Predicts Failures on a Semi-naturalistic Measure of Health Care Compliance

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Abstract

HIV-associated neurocognitive impairment, particularly in the domain of prospective memory (ProM), increases the risk of poor everyday functioning outcomes, including medication non-adherence. However, whether ProM plays a role in health care compliance outside of the realm of medication adherence remains to be determined. This study evaluated the hypothesis that ProM is an independent predictor of failure to comply with non-medication related instructions akin to those commonly given by health care providers. Participants were 139 HIV-infected adults who underwent medical, psychiatric, and neuropsychological assessments, including a laboratory-based measure of ProM. To assess real-world compliance, participants were instructed to call the examiner 24 hours after the evaluation and report how many hours they had slept. Individuals who failed to correctly comply with these instructions (n=104) demonstrated significantly lower performance on both time- and event-based ProM at baseline than the compliant group (n=35), an effect that was primarily driven by errors of omission. ProM remained a significant predictor of noncompliance after controlling for potential confounders, including demographics (e.g., education), traditional cognitive measures of retrospective memory and executive functions, and psychiatric factors (e.g., depression). Results support the hypothesis that ProM plays a unique role in compliance with health care instructions for HIV disease management and may inform interventions designed to improve treatment outcomes.

Keywords

Episodic memory; AIDS dementia complex; compliance; adherence; everyday functioning; human immunodeficiency virus

Adherence to medical treatment has been defined by the World Health Organization (WHO) as the extent to which a person's behavior corresponds to agreed-upon recommendations from a health care provider (WHO, 2003). While much of the existing research on medical adherence has focused specifically on medication-taking behavior, the term "adherence" (or

“compliance”) encompasses a wide variety of health-related behaviors, including seeking medical attention, obtaining immunizations, attending follow-up appointments, improving personal hygiene, diet, and levels of exercise as well as reducing risk behaviors such as smoking and unprotected sex.

Chronic medical conditions such as cardiovascular disease, diabetes, and HIV/AIDS are expected to exceed 65% of the global burden of illness in 2020 (WHO, 2003). Commonly prescribed treatments for chronic illness include pharmacological therapies, therapeutic diets, and therapeutic exercise. Due to poor compliance, however, an estimated one half of patients prescribed these remedies in the United States fails to obtain the intended clinical benefits (Dunbar-Jacob, Erlen, Schlenk, Ryan, Sereika, et al., 2000). Failure to comply with medical instructions can lead to more frequent hospital visits, reduced quality of life, increased morbidity, and worse clinical outcomes, including higher mortality rates (Osterberg & Blaschke, 2005). Moreover, high rates of non-compliance and the potential for clinical consequences are evident in a wide variety of therapeutic scenarios, including emergency room discharge (e.g., Engel, Heisler, Smith, Robinson, Forman, et al., 2009) and post-surgery instructions (e.g., Toussi, Fujioka, & Coleman, 2009). Health care providers’ effectiveness managing chronic conditions is heavily dependent upon the patient’s ability to schedule and attend laboratory and medical visits, follow through with recommendations for behavior change and activities intended to prevent disease and promote health, and comply with symptom reporting and monitoring directions (e.g., medication side effects).

Specifically with regard to HIV/AIDS, suboptimal compliance may result in a number of adverse consequences, which in turn may lead to poorer disease outcomes. For example, a missed medical appointment deprives a provider of an opportunity to diagnose and treat opportunistic infections or side effects from antiretroviral therapy (ART) and from delivering critical secondary HIV prevention education. Missed laboratory appointments may result in fewer biological samples from which to monitor changes in viral load and CD4 cell counts. Suboptimal ART adherence can lead to increases in viral load and the progression to AIDS, as well as to drug-resistant strains of HIV and a heightened likelihood of transmitting the virus to others (e.g., Bangsberg, Perry, Charlebois, Clark, Robertson, et al., 2001). While a great deal of research attention has been focused on medication adherence in HIV disease, few studies have examined predictors of medical compliance with reference to general health behaviors, such as following medical instructions.

Treatment for HIV infection involves a singularly strict and oftentimes complicated medication regimen, requiring multiple visits each year to a provider possibly over the course of a lifetime. A number of factors may influence an HIV-infected individual’s ability to comply with these requirements, including demographics (e.g., ethnicity), health beliefs (e.g., attitudes toward medicine), disease severity (e.g., nadir CD4 count), psychiatric symptoms (e.g., depression), social variables (e.g., social support), and environmental factors (e.g., use of compensatory strategies) (e.g., Chesney, Ickovics, Chambers, Gifford, Neidig, et al., 2000). In addition, neurocognitive impairment, particularly in executive functions and retrospective memory, can double the risk of non-adherence to ART (Hinkin, Castellon, Durvasula, Hardy, Lam, et al., 2002).

Research has demonstrated that prospective memory (ProM) also plays a critical role in the ability of HIV-infected patients to comply with medical instructions (e.g., Contardo, Black, Beauvais, Dieckhaus, & Rosen, 2009; Woods, Iudicello, Moran, Carey, Dawson, et al., 2008a; Woods, Moran, Carey, Dawson, Iudicello, et al., 2008b; Woods, Dawson, Weber, Gibson, Grant, et al., 2009). ProM, a form of episodic memory, refers to the ability to perform an intended action in the future (Kvavilashvili & Fisher, 2007). Successful ProM requires a number of component cognitive processes, including independently detecting

environmental cues initially associated with performing the intention (e.g., the passage of time or the occurrence of an event, such as eating breakfast), disengaging from an ongoing task (e.g., normal daily activities), and retrieving the associated intention from retrospective memory (RetM). The detection and retrieval processes occur in the context of ongoing distraction and without explicit reminders (Carey, Woods, Rippeth, Heaton, & Grant, 2006). This is in contrast to RetM, which is the ability to remember information from past events and which is prompted by an explicit request (e.g., recalling the name of a particular medication). While both ProM and RetM are components of episodic memory, ProM is theorized to be the stronger contributor to the performance of instrumental activities of daily living (IADLs), including compliance with medication instructions, due to its greater reliance on self-initiated detection and retrieval processes (Park & Kidder, 1996; Woods et al., 2008a).

Researchers have provided fairly consistent evidence of ProM's dissociation from other cognitive functions often impaired in HIV, including RetM and working memory, despite conceptual overlap. This work has begun to specify the component processes responsible for ProM's effect on functional outcomes and more generally, ascertain the distinctiveness of the construct of ProM. Gupta and colleagues compared five confirmatory structural equation models evaluating competing hypotheses regarding the dissociability of ProM from RetM, executive functions, and motor functions in an HIV cohort. The authors found that the model in which ProM loaded on a unique factor represented the data the better than the other models, including one that hypothesized a general factor driving performance across all neurocognitive measures and several models hypothesizing that ProM is better characterized by other domains of cognitive functioning (Gupta, Woods, Weber, Dawson & Grant, in press). In an exploratory factor analysis, Contardo and colleagues observed that measures of ProM loaded most strongly on factors distinct from RetM, executive functioning, and processing speed (Contardo et al., 2009). Researchers have observed moderate correlations between RetM and ProM (e.g., Contardo et al., 2009; Gupta et al., in press; Martin et al., 2007; Woods et al., 2007), executive function/attention and ProM (e.g., Carey et al., 2006; Gupta et al., in press), and between working memory and ProM (e.g., Carey et al., 2006) indicating that these abilities are related but also distinct in people living with HIV.

Studies suggest that HIV-infected individuals subjectively experience more ProM failures in their daily lives (Woods, Carey, Moran, Dawson, Letendre, et al., 2007) and perform more poorly on laboratory measures of ProM (Carey et al., 2006; Martin, Nixon, Pitrak, Weddington, Rains, et al., 2007) than their seronegative counterparts. Specifically, HIV-associated ProM deficits are found on both time-based (i.e., remembering to perform a task at a particular time; Martin et al., 2007; Carey et al., 2006) and event-based (i.e., remembering to perform a task after recognizing an external cue; Carey et al., 2006) ProM tasks. Moreover, time-based ProM impairment could not be attributed to comorbid conditions related to substance dependence or generalized deficits in episodic memory (Martin et al., 2007). Increased rates of omission (i.e., no response) and loss of time errors (i.e., the correct intention performed at the wrong time) in the context of normal recognition suggest that HIV leads to difficulties with strategic encoding and retrieval rather than problems of consolidation or other failures of RetM, a pattern consistent with damage to frontostriothalamocortical networks (Carey et al., 2006).

From a clinical perspective, HIV-associated ProM deficits are associated with a fourfold greater likelihood of concurrent declines IADL dependence than RetM (Woods et al., 2008a) and are highly predictive of a number of adverse behaviors, including risky sexual and injection practices (Martin et al., 2007). In addition, objective measures of ProM display incremental ecological validity regarding successful daily functioning among HIV-infected individuals and independently predict IADLs beyond the influence of traditional measures

of neuropsychological impairment, affective distress, demographics, and other key variables (e.g., HIV disease severity; Woods et al., 2008a). Specifically with regard to medication management, research has demonstrated that objective and self-reported measures of ProM explained unique variance relative to cognitive psychiatric, psychosocial, and environmental predictors of adherence (Woods et al., 2008b). Two recent studies using medication event monitoring systems (MEMS) to measure medication adherence extended this earlier work, finding that ProM predicted adherence independently of known risk factors (Contardo et al., 2009; Woods et al., 2009). For example, Woods and colleagues reported that HIV-infected individuals who committed at least one time-based ProM error were almost six times as likely to be nonadherent at one-month follow-up as compared to those with no errors (Woods et al., 2009).

Collectively, findings support the hypotheses that impaired ProM increases the risk of medication non-adherence and dependence in IADLs. Questions remain, however, as to whether ProM predicts semi-naturalistic measures of compliance outside of the realm of medication adherence, such as with medical instructions of the sort commonly received from a provider. One scenario with clear clinical relevance arises when a physician requests a telephone call from a patient subsequent to the patient undergoing lumbar puncture. Under circumstances very like those attending the compliance task reported in this study, patients are routinely asked to call the medical office within 24 hours post-surgery to report any emergent symptoms. Although general medical compliance of this kind may be related to medication management (Woods et al., 2008b), these two constructs are not identical. Indeed, it may be argued that telephone tasks capture a form of compliance that is driven by factors other than, or in addition to, those that drive medication adherence. For example, Hertzog and colleagues did not observe a correlation between performance on a telephone task and objective or self-reported measures of adherence among adults with rheumatoid arthritis (Hertzog et al., 2000). Among individuals with HIV/AIDS, a 24-hour telephone task likewise was not related to HIV antiretroviral adherence measured using MEMS (Woods et al., 2009). Two important distinctions between these constructs are chronicity and frequency; that is, while medication adherence is typically viewed as a habitual behavior occurring at regular intervals (particularly for treatment of HIV), telephoning a health care provider is much more infrequent and sporadic. Thus, there may be important differences in the cognitive, psychiatric, and psychosocial predictors of these two different aspects of compliance.

Research identifying novel, salient clinical predictors of compliance with medical instructions is important and may serve to improve early identification and remediation of potential barriers to compliance. This study examined clinical predictors of compliance with a task meant to mimic “real life” circumstances under which HIV-infected patients might be asked to comply with general medical instructions (i.e., making a telephone call to the laboratory one day after a research appointment to provide information on the number of hours slept the night after the examination; see Carey et al., 2006). This semi-naturalistic measure of compliance incorporated a longer delay between intention formation and execution than is typical for most laboratory-based measures and provided no reminders or cues to prompt intention retrieval. Consistent with the general HIV adherence literature, it was hypothesized that (1) greater HIV disease severity, higher levels of affective distress, demographics (e.g., lower education), and general neurocognitive impairment would predict compliance among a sample of HIV-infected individuals, and (2) non-compliant individuals would demonstrate lower performance on a standardized, laboratory-based measure of ProM as compared to compliant participants, even after considering the effects of the above-noted traditional predictors of adherence.

Method

Participants

Participants were 139 HIV-infected men and women recruited via flyer or newspaper advertisement from the San Diego community or local HIV clinics. The study was approved by the institution's human research protections program. Exclusion criteria were severe psychiatric illness (e.g., schizophrenia), neurological disease (e.g., seizure disorders, stroke, closed head injury with loss of consciousness for more than 15 minutes, and central nervous system neoplasms or opportunistic infections), verbal IQ scores <70 (based on Wechsler Test of Adult Reading [WTAR]; Psychological Corporation, 2001), a diagnosis of substance dependence within six months prior to the baseline evaluation, and a urine toxicology screen positive for illicit drugs on the day of testing. Table 1 shows the demographic, HIV disease, psychiatric, and neuropsychological characteristics of the entire study cohort. The participants were generally middle-aged, Caucasian men with post-high school educational backgrounds and fairly well managed HIV disease (e.g., the median CD4 t-lymphocyte count was over 500). About half of participants were diagnosed with substance dependence during their lifetime. In addition, nearly half of the participants were diagnosed with current major depressive disorder, with only a small percentage meeting lifetime criteria for generalized anxiety disorder.

Materials and Procedure

After providing written informed consent, participants completed a comprehensive neuropsychological, psychiatric, and medical evaluation for which they received nominal monetary compensation. Prior to beginning their neuropsychological assessment, each participant was instructed to telephone the examiner at a specific time the following day and leave a voice mail message specifying the number of hours slept the previous night (Carey et al., 2006). Although not explicitly mentioned or encouraged by the examiner, the use of mnemonic strategies such as electronic calendars was not restricted. Performance on this semi-naturalistic measure was the dependent variable of interest; participants leaving a message the next day at the correct time containing the correct information were classified as "Compliant" ($N = 35$). Those who either did not leave a message, did so at an incorrect time ($\geq 15\%$ of the 24 hr target time), or left a message containing information other than the number of hours slept were classified as "Non-compliant" ($N = 104$). About 40% of these ($N = 41$) placed the telephone call but did so at the wrong time or left the wrong message. Note that, telephone call-in tasks have been used extensively in prospective memory research (e.g., Devolder, Brigham & Pressley, 1990; Hertzog et al., 2000; Kvavilashvili & Fisher, 2007) and are a typical feature of paradigms commonly used in semi-naturalistic settings (McDaniel & Einstein, 2007). However, although this measure has been evaluated in previous studies as an adjunct trial of the Memory for Intentions Screening Test (MIST), it is in fact an optional component and is not factored into the MIST summary score, component process scores, or error scores. It therefore meets the statistical requirements for a criterion variable in our logistic regression analysis (described in the Results section below). Prior research shows that failure on this 24-hour compliance measure is prevalent in HIV infection (Carey et al., 2006) and is associated with poorer medication management (Woods et al., 2008b).

Prospective memory assessment—Performance-based ProM was assessed using the Memory for Intentions Screening Test (MIST; Raskin, 2004), which is a 30-minute, eight-trial test during which participants completed a series of word search puzzles as the ongoing distractor tasks. A MIST summary score, time-based score, event-based score, distractor task score, recognition score, and retrieval index were calculated. Errors were coded as no response (i.e., response omission errors), loss of time (i.e., executing an intention $\geq 15\%$ of

the target time), task substitution (e.g., responding verbally instead of with an action or vice versa), or loss of content (i.e., awareness that a response is required but failure to recall the content). The overall score (i.e., MIST Summary score) ranges from 0–48 (Raskin, 2004; see Woods et al., 2008c for more a detailed description of the MIST variables). Published evidence supports the reliability (Woods, Moran, Dawson, Carey & Grant, 2008c) and construct validity (Woods et al., 2008a, 2008c) of the MIST. Participants also completed the 8-item Prospective Memory Scale from the Prospective and Retrospective Memory Questionnaire (PRMQ; Smith et al., 2000) as an indicator of self-reported ProM complaints.

General neuropsychological assessment—Participants also completed a standard battery of clinical tests of neuropsychological functioning. The battery was consistent with National Institutes of Health guidelines for assessing the cognitive domains that are most sensitive to HIV infection (Antinori, Arendt, Becker, Brew, Byrd, et al., 2007). The specific domains assessed were retrospective learning and memory (immediate and long delayed trials of the California Verbal Learning Test – Second edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) and the Rey-Osterreith Complex Figure (Stern, Javorsky, Singer, Singer Harris, Somerville, et al., 1999)), information processing speed (Trail Making Test, Part A (TMT; Reitan & Wolfson, 1985) and total execution time from the Tower of London – Drexel (ToL-DX; Culbertson & Zillmer, 2001)), executive functions (TMT Part B and the ToL-DX total move score), attention/working memory (Digit Span subtest from the Wechsler Adult Intelligence Scale – Third Edition (The Psychological Corporation, 1997)) and the total errors from the self-ordered pointing test (SOPT; Morgan, Woods, Weber, Dawson, Carey et al., 2009), verbal fluency (animals (Benton, Hamsher, & Sivan, 1994) and actions (Woods, Scott, Sires, Grant, Heaton et al., 2005)), and motor coordination (Grooved Pegboard test; Kløve, 1963). Raw scores were converted to population-based *z* scores derived from the current study sample (*N* = 139) then averaged across the tests in each domain to create composite *z* scores for each ability area.

Psychiatric assessment—Lifetime and current diagnoses of major depressive disorder, generalized anxiety disorder, and substance use disorders were generated from structured psychiatric interviews conducted using the Composite International Diagnostic Interview (version 2.1; WHO, 1998) according to Diagnostic and Statistical Manual of Mental Disorders criteria (4th ed., American Psychiatric Association, 1994). These CIDI modules were chosen because they assess the psychiatric disorders most prevalent in HIV disease. Participants also completed the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1981), which measures current affective distress in the areas of tension/anxiety, depression/dejection, anger/hostility, vigor/activity, fatigue/inertia, and cognitive/confusion. The POMS also provides a Total Mood Disturbance score on which higher scores signal greater distress.

Results

As shown in Table 1, bivariate analyses revealed that participants who did not comply with instructions to leave a telephone message were less likely to be Caucasian ($p < 0.01$) than their compliant counterparts and had completed on average one fewer years of education ($p = 0.02$), though both groups were highly educated ($M = 14$ years, $SD = 2.3$). No group differences were evident on measures of disease characteristics, including duration of HIV infection, current or nadir CD4 count, and AIDS diagnosis ($ps > 0.20$). Overall affective distress (i.e., Total Mood Disturbance) was marginally higher among non-compliant participants ($p = 0.08$). Post-hoc tests conducted on the POMS subscales showed significant group differences in the expected directions on depression/dejection ($p = .01$) and anger/hostility ($p = .02$). Trend-level differences also emerged on the tension/anxiety ($p = .09$) and

cognitive/confusion ($p = .08$) subscales, but no significant group findings were present for the vigor/activation or fatigue/inertia scales ($ps > .20$).

Table 1 also displays the neurocognitive domain z-scores for the compliant and non-compliant groups. Group differences were observed in the expected direction for the executive functioning ($p = .004$, Cohen's $d = -.58$), working memory ($p = .009$, $d = .53$), and RetM ($p = .049$, $d = .45$) domains. No other cognitive domain was significantly different between the two study groups ($ps > .10$).

Table 2 displays the results for each group on the MIST and PRMQ variables of interest. Independent samples t-tests revealed no significant between-groups differences on any of the PRMQ variables ($ps > 0.10$). The MIST variables were negatively skewed (Shapiro-Wilk $ps < 0.05$), so Wilcoxon rank-sum tests were used to compare compliant and non-compliant groups on all of the ProM scores. Participants who did not comply with instructions to leave a telephone message performed significantly worse on the MIST summary score than the compliant group ($p < 0.01$, Cohen's $d = -0.58$), scored lower on both the time- and event-based subscales ($ps < 0.05$, Cohen's $ds = -0.41$ and -0.55 , respectively) and the retrieval index ($p = 0.02$, Cohen's $d = 0.50$), and committed more "no response" errors ($p < 0.05$, Cohen's $d = 0.40$). Non-compliant individuals also performed more poorly on the recognition trial but only marginally so ($p = 0.05$, Cohen's $d = -0.36$).

To determine whether ProM was an independent predictor of compliance, a binary logistic regression was conducted with group membership as the dependent variable. Predictors were the MIST summary score and factors that differed between groups in bivariate analyses (i.e., education, ethnicity, POMS depression/dejection and anger/hostility subscales, and neurocognitive z-scores from the domains of executive functions, working memory, and retrospective memory). The overall model was significant ($\chi^2 [8, 132] = 27.9$, $p < 0.001$), with the MIST summary score emerging as the sole independent predictor of compliance ($\chi^2 = 6.1$, $p = 0.01$). The range odds ratio for the MIST summary score was 20 (95% confidence interval = 2, 352). Education ($\chi^2 = 3.8$, $p = 0.05$) contributed to the model at a trend-level; however, no other variable was significantly associated with compliance in this final model (all other $ps > 0.10$).

In post hoc analyses, we further evaluated whether compliance as measured using the 24-hr call-in task represented a unitary construct or whether different types of responses (i.e., not calling at all versus not placing the call within a 24-hour time period) reflected different kinds of non-compliance behavior potentially supported by different underlying processes. Non-compliant participants were divided into two groups according to whether they placed a call at the wrong time or did not place a call at all. Wilcoxon rank-sum tests and logistic regression analyses similar to those described above were then conducted using three groups rather than two. Results were consistent with those reported here and suggested a unitary construct; specifically, non-compliant participants who called at the wrong time and non-compliant participants who did not place the call each performed significantly worse than the compliant group on the MIST summary score, the time-based and event-based subscales and the retrieval index and committed more "no response" errors ($ps < .05$). The MIST summary score emerged as the sole independent predictor of compliance in a multinomial logic regression ($p < .05$). Finally, we evaluated these comparisons using a continuous measure of compliance rather than dichotomous group membership (Y/N), and again, results were similar ($p < .05$). In sum, no matter how the compliance variable was analyzed, results remained the same.

Discussion

To our knowledge, this is the first study in an HIV-infected cohort to evaluate the clinical predictors (i.e., neurocognitive, demographic, psychiatric, and disease) of compliance with general medical instructions of the kind frequently given by health providers. The semi-naturalistic compliance measure used here accommodated “real-world” conditions, including a delay of several hours before the instructed behavior was to take place and made no restrictions (or recommendations) on the types of mnemonic strategies that participants could employ. The ability to follow these kinds of instructions while concurrently managing the distractions of daily life may be as relevant to HIV disease progression as is medication adherence (e.g., Toussi, Fujioka, & Coleman, 2009). A patient’s tendency to skip laboratory and medical visits or otherwise disregard medical directives could limit a provider’s ability to meaningfully prescribe medication, monitor its effects, and modify regimens as indicated. Indeed, medical appointment attendance *predicted* MEMS-measured medication adherence in a sample of HIV-positive patients with serious mental illness (Wagner, Kanouse, Koegel, & Sullivan, 2004). The degree of patient compliance with provider-recommended health promoting and disease preventing behaviors is likely to be critically associated with clinical outcomes and quality of life.

Consistent with our hypothesis, HIV-associated ProM deficits were associated with a reduced likelihood of successfully executing the 24-hour call-in task independently of other significant predictors. Individuals with the lowest summary score on the MIST (i.e., 15) were 20 times more likely to be non-compliant than those with the highest scores (i.e., 48). In fact, ProM performance as measured by the MIST summary scale was the *only* predictor of compliance when evaluated in multivariate models that included factors associated with compliance in bivariate analyses (i.e., demographics, other cognitive functions, and affective distress). This is consistent with other research among HIV-infected individuals in which ProM has emerged as a unique and independent predictor of IADLs (Woods et al., 2008a), medication management (Woods et al., 2008b), and medication adherence (Contardo et al., 2009; Woods et al., 2009). Results also support the hypothesis that ProM represents a unique aspect of cognition that influences clinically important behaviors and that may not be fully captured by traditional neurocognitive measures, such as tests of executive functions.

On average, non-compliant participants performed more poorly on both time- and event-based tasks and on the retrieval index and committed significantly more omission errors (i.e., no response) than compliant individuals. This pattern was observed in conjunction with normal performance on the distracter task and only a trend-level finding for recognition, which was associated with a small effect size (cf. the medium effect size for the MIST summary score). Other researchers have reported similar ProM profiles among HIV-infected individuals, suggesting that noncompliance is driven, at least in part, by impaired cue detection and self-initiated intention retrieval (e.g., Woods et al., 2008a, 2008b, 2009). In other words, non-compliant HIV-infected individuals seem to experience difficulty allocating the cognitive resources necessary to complete a distracter task while simultaneously monitoring the environment for the time- or event-based cues that might trigger intention retrieval (see McDaniel & Einstein, 2000). The present results also suggest that mild encoding and/or consolidation deficits, as evidenced by the trend-level finding on the recognition task, may also have played a role in non-compliance. This possibility is further supported by the mild deficits in delayed RetM evident in the non-compliant group. Prospective experimental work is needed to gain a clearer picture of the possible role of these factors in compliance, as the MIST does not allow one to readily draw such conclusions regarding these component processes.

As measured by the PRMQ, self-reported frequency of ProM failures was not predictive of compliance with the 24-hour task. This finding is consistent with prior research showing that PRMQ is insensitive to performance-based deficits in ProM (Woods et al., 2007) and medication non-adherence as measured by medication event monitoring system caps (Woods et al., 2009). Thus, although HIV is associated with elevated PRMQ complaints (Woods et al., 2007), which are strongly predictive of *self-report* declines in IADLs (Woods et al., 2008a) and medication management (Woods et al., 2008b), the PRMQ is nevertheless not associated with performance-based cognitive or functional outcomes. Such findings highlight the need for cautious interpretation of relationships between self-report measures and speak to the importance of incorporating performance-based tests of ProM in studies of everyday functioning in HIV disease.

Consistent with previous adherence research (e.g., Hinkin et al., 2002), lower performance on measures of working memory, executive functions (i.e., planning and divided attention) and retrospective memory was also associated with non-compliance on the 24-hour telephone task. Research has shown that impairment in these ability areas doubles the risk of ART non-adherence among people living with HIV (Hinkin et al., 2002), even in statistical models that include measures of psychiatric distress and disease severity. Executive dysfunction and episodic memory deficits have also been linked to dependence in other aspects of everyday functioning, such as automobile driving (e.g., Marcotte, Heaton, Wolfson, Taylor, Alhassoon, et al., 1999). That the RetM and executive function effects observed in the current study disappeared in multivariate analyses that included ProM provides further support for the notion that the execution of future intentions plays an important and unique role among cognitive abilities in supporting successful everyday functioning. Indeed, such data also converge with current theories of ProM (e.g., McDaniel & Einstein, 2007) which propose that this ability area may be an umbrella construct comprised of multiple component processes, including working memory, executive functions (e.g., planning), and RetM. In fact, our data provide support for the hypothesis that measures of RetM, working memory, and executive functioning represent a series of proxies for ProM in their effects on naturalistic noncompliance among people living with HIV.

Several additional factors predicted 24-hour compliance in bivariate analyses. Ethnicity emerged as a significant demographic predictor, such that compliant individuals were significantly more likely to be Caucasian. This is consistent with studies that have found lower rates of medication adherence among non-Whites across multiple medical contexts, including heart failure (Wu, Moser, Chung, & Lennie, 2008), pediatric renal transplant (Tucker, Petersen, Herman, Fennell, Bowling, et al., 2001), schizophrenia (Opolka, Rascati, Brown & Gibson, 2003), and HIV (Woods et al. 2008a). Ethnicity-based group differences in compliance may reflect the larger reality of health care in the United States, where non-Whites are at increased risk for disease acquisition and progression, worse clinical outcomes, reduced access to health care and lower life expectancy (Kaiser Family Foundation, 2009). Education level was also predictive of compliance, even within a relatively highly educated sample. This was surprising, as level of educational attainment tends not to be associated with adherence (e.g., Chesney et al., 2000; Woods et al., 2009). In fact, both education and ethnicity dropped to non-significance in multivariate models. Contrary to our hypothesis, disease severity was not significantly different between compliant and non-compliant groups, as has been shown in prior medication adherence studies in HIV cohorts (e.g., Woods et al, 2009). The most likely explanation for these divergent findings is that, while antiretroviral medications are directly related to biological outcomes in HIV disease, the measure used in this study is a semi-naturalistic proxy for general health compliance and therefore perhaps not optimally sensitive to biomarkers of disease severity. Alternatively, the range of our disease severity assessments was restricted in this generally healthy cohort (median CD4 count > 500), which may have limited our

ability to detect group differences on these variables. It is conceivable that those with more advanced illness might in fact outperform healthier counterparts on the 24-hour call-in task, since sicker individuals presumably see their providers more often and undergo more procedures, perhaps acquiring more mastery over compliance-related skills as a result (e.g., utilizing compensatory strategies). In any case, three of four hypothesized predictors were associated with the task, including demographics, affective distress, and general neurocognitive impairment, and data suggest the task is associated with other functional outcomes (Woods et al., 2008b). We therefore believe it is a reasonable proxy measure for general health-related compliance despite its lack of association with disease severity. Future studies should ensure a broader range of disease severity is included in the cohort.

Global acute affective distress, on the other hand, was marginally associated with non-compliance. In particular, non-compliant individuals were significantly more likely than their compliant counterparts to endorse higher levels of depression and hostility. This finding is consistent with previous reports that greater affective distress, particularly depression, is a strong predictor of important everyday functioning outcomes in HIV, including vocational functioning (e.g., Rabkin, McElhiney, Ferrando, van Gorp, & Lin, 2004), IADLs (Heaton et al., 2004), and non-adherence (e.g., Remien, Hirky, Johnson, Weinhardt, Whittier, et al, 2003; Yun, Maravi, Kobayashi, Barton, & Davidson, 2005). There has been less data on the possible relationship between anger/hostility and adherence, but one recent study showed that individuals with higher levels of trait anger and lower anger control were at risk for non-adherence (Leombruni et al., 2009). Future ProM studies might attend more to character and temperament factors, as they are likely to make important contributions to compliance behavior. Again, however, the bivariate association between affective distress (i.e., anger and depression) and non-compliance disappeared in multivariate models, with ProM emerging as the sole predictor in this sample.

Semi-naturalistic measures of compliance have the advantage of superior ecological validity as compared to responses from self-report measures completed in research settings, which may be influenced by external confounding factors inherent to self-report (e.g., social desirability bias; Wagner & Miller, 2004). The potential importance of the measure used here is highlighted by its demonstrated association with everyday functioning outcomes in HIV, including medication adherence. For example, prior research shows that seronegative individuals are three times more likely than demographically comparable HIV-infected participants to comply with instructions to place the telephone call and leave a message (12% and 38%, respectively; Carey et al., 2006). Woods and colleagues (2008b) subsequently found that the 24-hour adjunct telephone trial was a unique predictor of self-reported medication management (as measured by the 20-item Medication Management Efficacy Scale of the Beliefs Related to Medication Adherence questionnaire; McDonald-Miszczak, Maris, Fitzgibbon, & Ritchie, 2004), explaining 37% of the variance together with the time- and event-based MIST subscales and a self-reported summary measure of ProM (Woods et al., 2008b; cf. Hertzog et al., 2000).

The focus on a semi-naturalistic measure of compliance in this study was a unique and important aspect of the design but also its main limitation. Single-item naturalistic tests can be vulnerable to ceiling effects so that individual differences in performance are difficult to detect. While ceiling effects have been observed in studies with HIV-uninfected samples (Woods et al., 2008c), the present study suffered from a very low completion rate. About 75% of participants failed to telephone the research team as instructed (i.e., possible floor effects). Low completion rates on this task have been evident among other HIV+ samples (e.g., Carey et al., 2006) and among individuals with mild aging-related cognitive impairment (Karantzoulis, Troyer, & Rich, 2009). It is possible some participants did not actually *intend* to place the telephone call, as we did not include measures of intention

strength (nor have other studies using the 24-hour call-in measure, to our knowledge). Alternatively, participants may not have ascribed much importance to a research-related telephone call, or at least not as much as they might to other health care activities. Yet despite possible floor effects, our sample size was sufficiently large to provide adequate power to detect medium effect size differences between compliant and non-compliant respondents on several variables (i.e., ProM, demographics, and affective distress). A related limitation, shared with field-based measures in general, was the inability to control or evaluate possible confounding effects of unmeasured extraneous variables. We did not determine, for instance, whether participants used mnemonic devices (e.g., electronic calendars) to prompt recall or whether such strategies were effective. In addition, because we elected to administer only the modules of the CIDI that assess psychiatric conditions most prevalent in HIV, specifically major depressive disorder, generalized anxiety disorder, and substance use disorders, we did not collect data on the potential effects of other conditions that might be associated with cognitive deficits, including ADHD, bipolar disorder, and PTSD. Moreover, because middle-aged, highly-educated Caucasian men with well-managed disease were overrepresented in our cohort, results may not generalize to other groups burdened by HIV, such as economically disadvantaged people of color. Yet given the current results and the relevance to clinical outcomes of patient compliance, research to determine the construct validity of the 24-hour call-in task and identify additional confounders is warranted. Future studies might test hypotheses within a more demographically diverse cohort and report on the effect of intention strength, a wider range of psychiatric conditions, and the relative value participants place on following experimenter instructions as opposed to those from a medical provider. The effects of unmeasured extraneous variables might be documented using diary techniques or self-report.

This work broadens the scope of existing research by providing evidence that the documented effects of ProM specifically on medication adherence may generalize to other compliance-related behaviors, including following instructions of the kind frequently given by medical providers. ProM impairment appears to increase the risk of noncompliance with 24-hour call-in instructions even after considering general cognitive impairment, psychiatric comorbidity, and demographic characteristics. Research is needed to develop ProM-based intervention strategies and determine whether they might improve compliance with non-medication-related treatment as well as medication adherence. ProM-based strategies may attempt to strengthen the cue-intention encoding process (e.g., with implementation intentions; Gollwitzer & Brandstatter, 1997), improve strategic monitoring capability (e.g., provide training to redirect attention away from the ongoing task or other distractions to the ProM cue; McDaniel & Einstein, 2007), or reduce the need for strategic monitoring by reducing cognitive load (e.g., educate patients on the use of compensatory strategies such as setting an alarm; Raskin & Sohlberg, 2009). ProM has emerged as an important predictor of medical compliance, and a better understanding of how to address its effects will be of great clinical value.

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Table 1

Demographic, HIV disease, and Psychiatric Characteristics of Study Participants

Variable	Total Sample (<i>n</i> = 139)	Compliant (<i>n</i> = 35)	Non-Compliant (<i>n</i> = 104)	<i>p</i> ^a	Cohen's <i>d</i>
Demographic Characteristics					
Age (years)	45.6 (8.5)	47.3 (9.7)	45.0 (8.0)	.223	.26
Education (years)	14.1 (2.3)	14.9 (2.2)	13.9 (2.3)	.023	.44
Sex (% men)	87.0%	88.9%	86.5%	.757	-
Ethnicity (% Caucasian)	61.2%	80.0%	54.8%	.008	-
HIV Disease Characteristics					
Estimated duration of infection (years)	15 (7, 21)	15 (8, 20)	15 (7, 21)	.618	-
Current CD4 Count ^b	526 (321, 783)	553 (320, 733)	524 (322, 795)	.964	-
Nadir CD4 Count ^b	140 (38, 300)	127 (27, 215)	176 (44, 323)	.191	-
HIV RNA plasma (log 10)	1.7 (1.7, 2.1)	1.7 (1.7, 2.1)	1.7 (1.7, 2.2)	.857	-
Proportion with AIDS	61.9%	71.4%	58.7%	.178	-
Proportion on HAART	81.3%	82.9%	80.8%	.388	-
Psychiatric Characteristics					
Substance dependence (lifetime)	50.4%	60.0%	47.1%	.186	-
Major depressive disorder	53.3%	51.4%	53.9%	.799	-
Generalized anxiety disorder	5.8%	8.6%	4.9%	.424	-
Profile of Mood States ^b					
Tension/anxiety	8 (4, 12)	6 (3, 10)	8 (4, 13)	.092	-
Depression/dejection	5 (1, 13)	2 (0, 10)	6 (2, 13)	.014	-
Anger/hostility	4 (1, 14)	3 (0, 5)	5 (1, 9)	.023	-
Vigor/activity	16 (12, 20)	16 (13, 21)	16 (11, 20)	.415	-
Fatigue/inertia	6 (3, 13)	6 (4, 13)	7 (3, 13)	.769	-
Cognitive/confusion	6 (3, 11)	4 (2, 8)	6 (3, 11)	.082	-
Total	49 (31, 68.5)	39 (24, 61)	53 (31.75, 71)	.076	-
Neuropsychological Characteristics ^c					
Working memory	0 (.84)	.32 (0.77)	-.11 (0.84)	.009	.53
Executive functions ^d	0 (.86)	-.33 (0.54)	.11 (0.93)	.004	-.58
Retrospective learning	0 (.77)	.20 (0.85)	-.06 (0.74)	.210	.33

Variable	Total Sample (n = 139)	Compliant (n = 35)	Non-Compliant (n = 104)	p^a	Cohen's d
Retrospective memory	0 (.79)	.27 (0.84)	-.09 (0.76)	.049	.45
Motor skills ^c	0 (.93)	-.14 (0.60)	.05 (1.02)	.560	-.23
Verbal fluency	0 (.78)	.16 (0.74)	-.06 (0.79)	.110	.29
Information processing speed ^c	0 (.83)	-.21 (0.63)	.06 (0.87)	.120	-.36

Note.

^a p -values represent between-group comparisons for compliant (n = 35) and non-compliant (n = 104).

^b median (upper quartile, lower quartile).

^c z -scores.

^d higher z -scores reflect worse performance.

Table 2

Prospective Memory Scores in Compliant and Non-compliant Samples

ProM Variable	Total Sample (n = 139)	Compliant (n = 35)	Non-compliant (n = 104)	p ^d	Cohen's d (95% CI)
MIST					
Summary Score	39.0 (33.0, 45.0)	42.0 (39.0, 45.0)	39.0 (33.0, 44.3)	0.004	-0.58 (-0.96, -0.18)
Time-based	6.0 (5.0, 7.0)	7.0 (6.0, 7.0)	6.0 (5.0, 7.0)	0.037	-0.41 (-0.80, -0.02)
Event-based	7.0 (6.0, 8.0)	8.0 (7.0, 8.0)	7.0 (6.0, 8.0)	0.006	-0.55 (-0.93, -0.16)
Errors					
No Response	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.037	0.40 (0.01, 0.78)
Loss of Time	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, .8)	0.477	0.14 (-0.25, 0.52)
Task Substitution	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.184	0.26 (-0.12, 0.65)
Loss of Content	0.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.992	0.11 (-0.27, 0.49)
Recognition Trial	8.0 (8.0, 8.0)	8.0 (8.0, 8.0)	8.0 (7.0, 8.0)	0.054	-0.36 (-0.74, 0.03)
Retrieval Index	2.0 (1.0, 3.0)	2.0 (1.0, 2.0)	2.0 (1.0, 4.0)	0.023	0.50 (0.11, 0.89)
Distractor	16.0 (13.0, 19.0)	16.0 (13.0, 19.0)	15.0 (12.0, 19.0)	0.322	-0.13 (-0.51, 0.25)
PRMQ					
ProM Total	19.8 (6.1)	19.3 (5.8)	19.9 (6.2)	0.553	0.10 (-0.29, 0.48)
Env cued	9.5 (3.2)	9.0 (2.9)	9.6 (3.3)	0.282	0.19 (-0.20, 0.57)
Self cued	10.3 (3.1)	10.3 (3.1)	10.3 (3.1)	0.934	0.00 (-0.38, 0.38)

Note.

^a p-values represent between group comparisons for Compliant (n = 35) and Non-compliant (n = 104).

Data presented are medians and interquartile ranges. CI = Confidence Interval; Env = environmentally. MIST = Memory for Intentions Screening Test. PRMQ = Prospective and Retrospective Memory Questionnaire. ProM = prospective memory.